

ATTACHMENT IV

*Marked up copy of
Claims*

Claims:

1. A pharmaceutical composition for the treatment of the risk factors of syndrome X of Reaven comprising as active ingredient a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin.
2. A pharmaceutical composition comprising an additional compound.
3. A pharmaceutical composition comprising an additional compound having an additional pharmaceutical effect.
4. A pharmaceutical composition according to Claim 2 or 3 wherein the additional compound is selected among carriers, solvents and emulgators.
5. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Octreotide.
6. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Vapreotide.
7. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Lanreotide.
8. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analogs of somatostatin are Cyclopeptide somatostatin analogues selected among :

Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]

Cyclo[N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe]

Cyclo[Pro-Ala-D-Trp-Lys-Thr-Phe]

Cyclo[Pro-Tyr-D-Trp-Lys-Thr-Phe]

Cyclo[Pro-Phe-D-Trp-Lys- β -aminobutyric-Phe]

Cyclo[N-Me-Ala-Phe-D-Trp-Lys-Thr-Phe]

Cyclo[Pro-Phe-D-Trp-Lys-Val-Phe]

Cyclo[D-Ala-D-Phe-D-Trp-L-Lys-D-Thr-N-Me-D-Phe]

Cyclo[Pro-Phe-D-Trp-Lys-Thr(Bzl)] (Bzl = (a))

Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]

Cyclo[Pro-D-Phe-D-Trp-Lys-Thr(Bzl)]

Cyclo[Ahep-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser]

(Ahep = (b) - [SEQ ID NO 1] -

Cyclo[Ahep-Phe-D-Trp-Lys-Thr(Bzl)]

Cyclo[Ahep-Phe-D-Trp-Lys-Thr]

Cyclo[Ahep-Phe-D-Trp-Lys-Ser(Bzl)]

Cyclo[Ahex-Phe-D-Trp-Lys-Thr(Bzl)]

(Ahex = (c))

Cyclo[Aoct-Phe-D-Trp-Lys-Thr(Bzl)]

(Aoct = (d))

Cyclo[Ala-Cys-Phe-D-Trp-Lys-Thr-Cys]

(a) Bzl = benzyl

(b) Ahep = 7-aminoheptanoyl

(c) Ahex = 6-aminohexanoyl

(d) Aoct = 8-amino-octanoyl;

9. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-ol
10. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH₂ (Nal = (1))
11. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH₂
12. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Thr-Cys]-Nal-NH₂
13. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Nal-NH₂ (Abu = (2))
14. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Ser-Cys]-Nal-NH₂
15. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH₂
16. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
c(Ahep-Trp-D-Trp-Lys-Thr-Phe) (Ahep = (3))
17. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH₂ (Cpa = (4))
18. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH₂

19. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH₂
20. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH₂
21. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH₂
22. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Ala-Phe-D-Trp-Lys-Ala-Nal-NH₂
23. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH₂
24. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH₂
25. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH₂
26. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are polypeptides of the formula:
X-Lys-Asn-Phe-Phe-A-Lys-Thr-Phe-Thr-Ser-Y
wherein A is L- or D-Trp,
X is H-(Aeg)_m-Cys- or H-(Aeg)_m-Ala-Gly-Cys-,
Y is -Cys-(Aeg)_n-OH or
X and Y taken together are a 2-aminoethyl-glycyl
group in the ring position and
m and n are 0, 1, 2, provided that
m and n are at least 1,
and their cyclic disulfide derivatives.
27. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are peptides of the formula:

Bmp-Lys-X-Phe-Phe-trp-Lys-Thr-Phe-Thr-Y-Cys-OH [SEQ ID NO 2]-
 3 4 5 6 7 8 9 10 11 12 13 14

in which

Bmp represents the desaminocysteine radical,
 X represents Asn,
 trp represents D-Trp that may be substituted
 in the benzene ring by a halogen atom, and
 Y represents the radical of an alpha-(lower
 alkyl)amino-(lower alkyl)-carboxylic acid
 having a minimum of 4 and a maximum of 8
 carbon atoms, in which the two lower alkyl
 radicals can be connected to one another with
 a single C-C bond, an oxygen atom or a sulphur (II)
 atom.

28. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are cyclic octapeptides of the formula

Asn-Phe-Phe-Trp-Lys-Thr-Phe-Gaba(Ar) [SEQ ID NO 3]-
 5 6 7 8 9 10 11 12

in which

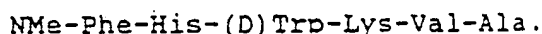
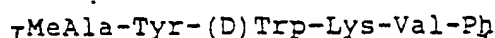
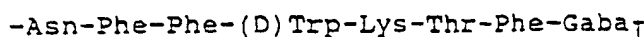
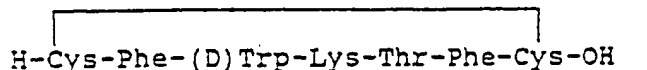
Trp represents L-Trp or D-Trp, in which the
 benzene ring may be substituted by a
 fluorine atom, and
 Gaba(Ar) represents the residue of α -aminobutyric
 acid substituted by a cyclic hydrocarbyl
 radical Ar selected from the group consisting
 of cyclohexyl; phenyl optionally substituted
 by halogen, nitro or phenoxy; and naphthyl
 optionally substituted by halogen.

29. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are compounds of formula

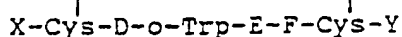
H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-R₁
 -Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-R₁₈-R₁₉-Phe-Phe-D

-Trp-Lys-Thr-R₂₅-R₂₆-R₂₇-R₂₈-OH wherein R₁ is

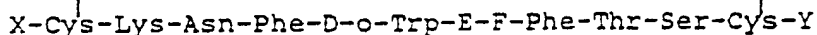
wherein the residues B, D and E have the L-configuration, and the residues in the 2- and 7-position and any residues Y_1 , 4) and Y_2 , 4) each independently have the (L)- or (D)-configuration and compounds of the following formulae



36. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analogs are Somatostatin analogs



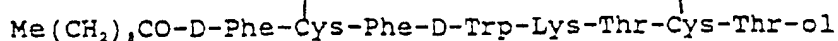
I-[SEQ ID NO 4]-



II-[SEQ ID NO 5]-

I, II, X = N-terminus anchor; Y = C-terminus anchor, G-I or its alc; wherein at least I of X, Y = cationic anchor; D = Phe Tyr, 3-(p-fluorophenyl)alanine or 3 (p-chlorophenyl)alanine residue; E = Lys, Lys(R^1); R^1 = C_{1-6} (fluoro)alkyl; F = Thr, Val, Ser; G = D- or L-Thr, Phe, or 3-(2-naphthyl)alanine residue; I = OH, NH_2 , NHR^1 .

37. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are peptides:
 $RR^1NCHR^2CONHCH(CH_2SR^4)CO-Phe-Trp-Lys-X-NHCHR^3CH_2SR^5$
 [R = inorg. or org. acyl group, R^1 = H, alkyl, $NCHR^2CO$ moiety = I.



I

or D-Phe (optionally ring substituted by halo, NO_2 , OH, alkyl, alkoxy); Phe, Trp, (D or L), may be ring substituted by NO_2 , NH_2 , OH, alkyl, alkoxy; Lys may be α -N-methylated and ϵ -N-alkylated; X = D- or L- α -amino acid residue optionally α -N-methylated; R^1 = CO_2H , CH_2OH , carbamoyl, R^4 = R^5 = H, R^4R^5

= bond]

38. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-X-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly

Cys-X¹-x²-Phe-Phe-D-Trp-Lys-Tys-Thr-X³-X⁴-X⁵-X⁶-OH

39. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Leu-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-

Cys-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr-Thr-Ser-Cys-OH

40. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is

c(Spacer-Phe-D-Trp-Lys-Thr)

Spacer may stand for:

- a) R, S- δ -Bn-o-AMPA
- b) R- α -Bn-NMe-o-AMPA
- c) Phe-Pro

41. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

H₂N-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH-[SEQ ID NO 6]-

42. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

H₂N-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH-[SEQ ID NO 7]-

43. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

D- β -Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂

44. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

Ac-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂

45. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Trp-NH₂

46. A pharmaceutical composition according to any of Claims 1 to